HLA-DRB1 gene

major histocompatibility complex, class II, DR beta 1

Normal Function

The *HLA-DRB1* gene provides instructions for making a protein that plays a critical role in the immune system. The *HLA-DRB1* gene is part of a family of genes called the human leukocyte antigen (HLA) complex. The HLA complex helps the immune system distinguish the body's own proteins from proteins made by foreign invaders such as viruses and bacteria.

The HLA complex is the human version of the major histocompatibility complex (MHC), a gene family that occurs in many species. The *HLA-DRB1* gene belongs to a group of MHC genes called MHC class II. MHC class II genes provide instructions for making proteins that are present on the surface of certain immune system cells. These proteins attach to protein fragments (peptides) outside the cell. MHC class II proteins display these peptides to the immune system. If the immune system recognizes the peptides as foreign (such as viral or bacterial peptides), it triggers a response to attack the invading viruses or bacteria.

The protein produced from the *HLA-DRB1* gene, called the beta chain, attaches (binds) to another protein called the alpha chain, which is produced from the *HLA-DRA* gene. Together, they form a functional protein complex called the HLA-DR antigen-binding heterodimer. This complex displays foreign peptides to the immune system to trigger the body's immune response.

Each MHC class II gene has many possible variations, allowing the immune system to react to a wide range of foreign invaders. Researchers have identified hundreds of different versions (alleles) of the *HLA-DRB1* gene, each of which is given a particular number (such as *HLA-DRB1**04:01).

Health Conditions Related to Genetic Changes

autoimmune Addison disease

Certain variations in the *HLA-DRB1* gene have been linked to an increased risk of developing an autoimmune disorder called autoimmune Addison disease. Autoimmune disorders occur when the immune system malfunctions and attacks the body's tissues and organs. In autoimmune Addison disease, the immune system attacks the adrenal glands, which are small hormone-producing glands located on top of each kidney. Loss of hormones produced by the adrenal glands leads to the features of the condition, which include extreme tiredness (fatigue), nausea, low blood pressure (hypotension), and abnormally dark areas of skin

(hyperpigmentation), especially in regions that experience a lot of friction such as the armpits, elbows, and knuckles. A particular *HLA-DRB1* gene variant called *HLA-DRB1*04:04* is the most well-known risk factor for autoimmune Addison disease.

Normally, the immune system responds only to proteins made by foreign invaders, not to the body's own proteins. In autoimmune Addison disease, however, an immune response is triggered by a normal adrenal gland protein; in about 85 percent of people with autoimmune Addison disease, the protein is 21-hydroxylase. 21-hydroxylase is found in the adrenal glands where it plays a key role in producing a variety of hormones that regulate many essential functions in the body. The prolonged immune attack triggered by 21-hydroxylase damages the adrenal glands (specifically the outer layers of the glands known, collectively, as the adrenal cortex), preventing hormone production. A shortage of adrenal hormones (adrenal insufficiency) disrupts several normal functions in the body, leading to the diverse features of autoimmune Addison disease. It is not clear how *HLA-DRB1*04:04* and other *HLA-DRB1* variations are involved in the inappropriate immune response that causes autoimmune Addison disease.

Graves disease

Hashimoto thyroiditis

idiopathic inflammatory myopathy

juvenile idiopathic arthritis

multiple sclerosis

Variations in the *HLA-DRB1* gene have been associated with an increased risk of developing multiple sclerosis. This condition affects the brain and spinal cord (central nervous system), causing muscle weakness, poor coordination, numbness, and a variety of other health problems. One variant of this gene, called *HLA-DRB1*15:01*, is the most strongly linked genetic factor for the risk of multiple sclerosis.

Because the *HLA-DRB1* gene is involved in the immune system, changes in it might be related to the autoimmune response and inflammation that damage nerves and the protective coating surrounding them (the myelin sheath), leading to the signs and symptoms of multiple sclerosis. However, it is unclear exactly what role *HLA-DRB1* gene variants play in development of multiple sclerosis. A combination of genetic and environmental factors is likely involved in this condition.

narcolepsy

psoriatic arthritis

rheumatoid arthritis

Several common variations of the *HLA-DRB1* gene are associated with a person's risk of developing rheumatoid arthritis. This disease causes chronic abnormal inflammation that primarily affects the joints. *HLA-DRB1* is one of several genes in the HLA complex that have been associated with rheumatoid arthritis; variations of this gene are the most significant known genetic risk factor for the disease.

The *HLA-DRB1* gene variations associated with an increased risk of rheumatoid arthritis affect single protein building blocks (amino acids) in the beta chain. These changes occur near the antigen-recognizing binding groove, which is the part of the protein that attaches (binds) to viral or bacterial peptides. This binding triggers the immune response that attacks foreign invaders. Although the mechanism by which *HLA-DRB1* gene variations increase the risk of rheumatoid arthritis is unclear, researchers suspect it is related to changes in peptide binding that stimulate an abnormal immune response. However, many other genetic and environmental factors also contribute to a person's overall risk of developing rheumatoid arthritis.

A few variations of the *HLA-DRB1* gene appear to decrease the risk of developing rheumatoid arthritis. It is unclear why these particular changes may be protective.

type 1 diabetes

Combinations of variations in the *HLA-DRB1* gene and other HLA genes affect the risk of type 1 diabetes. Type 1 diabetes is characterized by high blood sugar levels resulting from a shortage of the hormone insulin and is caused by autoimmune damage to insulin-producing cells in the pancreas.

Type 1 diabetes risk is most increased by two specific combinations of variations of the *HLA-DRB1* gene and other HLA genes called *HLA-DQA1* and *HLA-DQB1*. Combinations of HLA gene variants are called HLA haplotypes. One haplotype, written as *DRB1*03:01-DQA1*05:01-DQB1*02*, is called DR3. The other haplotype, written as *DRB1*04:01/02/04/05/08-DQA1*03:01-DQB1*02*, is called DR4. People at highest risk of developing type 1 diabetes have one copy of the DR3 haplotype and one copy of the DR4 haplotype in each cell. Other HLA haplotypes only mildly increase the risk of type 1 diabetes, while some haplotypes seem to protect against developing this condition. Variations in other genes and environmental factors are also thought to affect the risk of this complex disorder.

autoimmune disorders

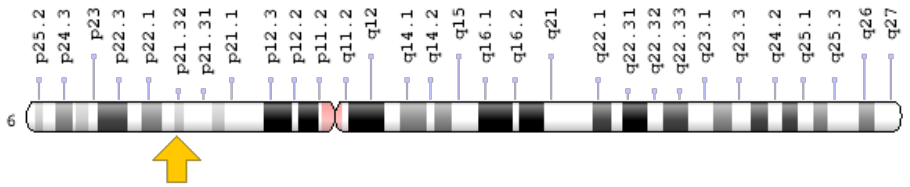
Normal variations of the *HLA-DRB1* gene have been associated with many other autoimmune disorders, including pemphigus, sarcoidosis, and others listed on this page. Pemphigus is a condition that causes severe blistering of the skin and mucous membranes (such as the moist lining of the mouth). Sarcoidosis is a disorder in which inflammation occurs in many organs and tissues of the body.

It is unclear how different versions of the *HLA-DRB1* gene influence the risk of developing autoimmune disorders. These disorders typically result from a combination of multiple environmental and genetic factors. Changes in other HLA and non-HLA genes, some of which remain unknown, also likely contribute to the risk of developing these complex conditions.

Chromosomal Location

Cytogenetic Location: 6p21.32, which is the short (p) arm of chromosome 6 at position 21.32

Molecular Location: base pairs 32,578,769 to 32,589,836 on chromosome 6 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- 2B1F_HUMAN
- 2B1G_HUMAN
- 2B13_HUMAN
- DRB1
- DRw10
- DW2.2/DR2.2
- HLA class II histocompatibility antigen, DR-1 beta chain
- HLA-DR1B
- HLA-DRB
- human leucocyte antigen DRB1
- lymphocyte antigen DRB1
- major histocompatibility complex, class II, DR beta 1 precursor
- MHC class II antigen

- MHC class II HLA-DR beta 1 chain
- MHC class II HLA-DR-beta cell surface glycoprotein
- MHC class II HLA-DRw10-beta
- SS1

Additional Information & Resources

Educational Resources

- Anthony Nolan Research Institute: Nomenclature for Factors of the HLA System
  http://hla.alleles.org/nomenclature/index.html
- Immunobiology (fifth edition, 2001): The Major Histocompatibility Complex and its Functions
  https://www.ncbi.nlm.nih.gov/books/NBK27156/
- The Merck Manual for Health Professionals: Human Leukocyte Antigen (HLA) System
  http://www.merckmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/human-leukocyte-antigen-hla-system

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28HLA-DRB1%5BTI%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D

OMIM

- MAJOR HISTOCOMPATIBILITY COMPLEX, CLASS II, DR BETA-1
  http://omim.org/entry/142857
- SARCOIDOSIS, SUSCEPTIBILITY TO, 1
  http://omim.org/entry/181000

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_HLA-DRB1.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=HLA-DRB1%5Bgene%5D
- HGNC Gene Family: C1-set domain containing
  http://www.genenames.org/cgi-bin/genefamilies/set/591

- HGNC Gene Family: Histocompatibility complex
  http://www.genenames.org/cgi-bin/genefamilies/set/588
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=4948
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/3123
- UniProt: 2B1F_HUMAN
  http://www.uniprot.org/uniprot/P01911
- UniProt: 2B1G_HUMAN
  http://www.uniprot.org/uniprot/Q29974
- UniProt: 2B13_HUMAN
  http://www.uniprot.org/uniprot/P01912
- UniProt: 2B17_HUMAN
  http://www.uniprot.org/uniprot/P13761

Sources for This Summary

- Alcina A, Abad-Grau Mdel M, Fedetz M, Izquierdo G, Lucas M, Fernández O, Ndagire D, Catalá-Rabasa A, Ruiz A, Gayán J, Delgado C, Arnal C, Matesanz F. Multiple sclerosis risk variant HLA-DRB1*1501 associates with high expression of DRB1 gene in different human populations. PLoS One. 2012;7(1):e29819. doi: 10.1371/journal.pone.0029819. Epub 2012 Jan 13.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22253788
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3258250/
- Aly TA, Ide A, Jahromi MM, Barker JM, Fernando MS, Babu SR, Yu L, Miao D, Erlich HA, Fain PR, Barriga KJ, Norris JM, Rewers MJ, Eisenbarth GS. Extreme genetic risk for type 1A diabetes. Proc Natl Acad Sci U S A. 2006 Sep 19;103(38):14074-9. Epub 2006 Sep 11.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16966600
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1563993/
- Chinoy H, Lamb JA, Ollier WE, Cooper RG. An update on the immunogenetics of idiopathic inflammatory myopathies: major histocompatibility complex and beyond. Curr Opin Rheumatol. 2009 Nov;21(6):588-93. doi: 10.1097/BOR.0b013e3283315a22. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19730377
- Gombos Z, Hermann R, Kiviniemi M, Nejentsev S, Reimand K, Fadeyev V, Peterson P, Uibo R, Ilonen J. Analysis of extended human leukocyte antigen haplotype association with Addison's disease in three populations. Eur J Endocrinol. 2007 Dec;157(6):757-61.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18057383

- Hor H, Kutalik Z, Dauvilliers Y, Valsesia A, Lammers GJ, Donjacour CE, Iranzo A, Santamaria J, Peraita Adrados R, Vicario JL, Overeem S, Arnulf I, Theodorou I, Jennum P, Knudsen S, Bassetti C, Mathis J, Lecendreux M, Mayer G, Geisler P, Benetó A, Petit B, Pfister C, Bürki JV, Didelot G, Billiard M, Ercilla G, Verduijn W, Claas FH, Vollenweider P, Waeber G, Waterworth DM, Mooser V, Heinzer R, Beckmann JS, Bergmann S, Tafti M. Genome-wide association study identifies new HLA class II haplotypes strongly protective against narcolepsy. Nat Genet. 2010 Sep;42(9):786-9. doi: 10.1038/ng.647. Epub 2010 Aug 15. Erratum in: Nat Genet. 2011 Apr;43(4):388. Vollenwider, Peter [corrected to Vollenweider, Peter].
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20711174
- OMIM: MAJOR HISTOCOMPATIBILITY COMPLEX, CLASS II, DR BETA-1 http://omim.org/entry/142857
- Noble JA, Valdes AM. Genetics of the HLA region in the prediction of type 1 diabetes. Curr Diab Rep. 2011 Dec;11(6):533-42. doi: 10.1007/s11892-011-0223-x. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21912932
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3233362/
- Prahalad S, Glass DN. A comprehensive review of the genetics of juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2008 Jul 21;6:11. doi: 10.1186/1546-0096-6-11.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18644131
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2515830/
- Raychaudhuri S, Sandor C, Stahl EA, Freudenberg J, Lee HS, Jia X, Alfredsson L, Padyukov L, Klareskog L, Worthington J, Siminovitch KA, Bae SC, Plenge RM, Gregersen PK, de Bakker PI. Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis. Nat Genet. 2012 Jan 29;44(3):291-6. doi: 10.1038/ng.1076.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22286218
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3288335/
- Rottembourg D, Deal C, Lambert M, Mallone R, Carel JC, Lacroix A, Caillat-Zucman S, le Deist F. 21-Hydroxylase epitopes are targeted by CD8 T cells in autoimmune Addison's disease. J Autoimmun. 2010 Dec;35(4):309-15. doi: 10.1016/j.jaut.2010.07.001. Epub 2010 Aug 3.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20685079
- Skinningsrud B, Lie BA, Lavant E, Carlson JA, Erlich H, Akselsen HE, Gervin K, Wolff AB, Erichsen MM, Løvås K, Husebye ES, Undlien DE. Multiple loci in the HLA complex are associated with Addison's disease. J Clin Endocrinol Metab. 2011 Oct;96(10):E1703-8. doi: 10.1210/jc.2011-0645. Epub 2011 Aug 3.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21816777
- Steck AK, Rewers MJ. Genetics of type 1 diabetes. Clin Chem. 2011 Feb;57(2):176-85. doi: 10.1373/clinchem.2010.148221. Epub 2011 Jan 4. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21205883
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4874193/
- Viatte S, Plant D, Raychaudhuri S. Genetics and epigenetics of rheumatoid arthritis. Nat Rev Rheumatol. 2013 Mar;9(3):141-53. doi: 10.1038/nrrheum.2012.237. Epub 2013 Feb 5. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23381558
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3694322/
- Yu L, Brewer KW, Gates S, Wu A, Wang T, Babu SR, Gottlieb PA, Freed BM, Noble J, Erlich HA, Rewers MJ, Eisenbarth GS. DRB1*04 and DQ alleles: expression of 21-hydroxylase autoantibodies and risk of progression to Addison's disease. J Clin Endocrinol Metab. 1999 Jan;84(1):328-35.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/9920103

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/HLA-DRB1

Reviewed: June 2014
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services